Ergot Intoxication:

Historical Review and Description of Unusual Clinical Manifestations

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Clinical ergotism as seen today results almost exclusively from the excessive intake of ergotamine tartrate in the treatment of migraine headache. Although both gangrenous and convulsive symptoms are seen in naturally occurring ergotism resulting from the ingestion of fungus infected rye, only gangrenous ergotism has been reported following the excessive ingestion of ergotamine tartrate. The symptoms of both iatrogenic and naturally occurring ergotism appear to result from regional ischemia caused by ergot induced vasospasm. This report discribes experiences in the diagnosis and management of two patients with unusual manifestations of iatrogenic ergotism. One patient presented with ischemia of all extremities and bilateral foot drop probably due to ischemic damage to the common peroneal nerves, a finding not previously described in ergot intoxication. The foot drop totally resolved in several months following the discontinuation of ergot. A second patient presented with unilateral leg ischemia and transient monocular blindness, both of which resolved after discontinuation of ergot. Both patients displayed typical angiographic findings of ergotism. There is no convincing evidence that any treatment other than discontinuation of ergotamine is of benefit in the treatment of iatrogenic ergotism.

ERGOTISM, which once occurred in great epidemics, has virtually disappeared since recognition of the etiology of the naturally occurring disease. Epidemic ergotism has been largely replaced by ergotism resulting from the medicinal use of the ergot alkaloids. Iatrogenic ergotism, although occurring infrequently, often presents a diagnostic problem. For a physician to encounter a case of classic ergotism is sufficiently unusual to make the diagnosis difficult, and for him to encounter a patient with an unusual manifestation of ergotism, possibly without a clear history of drug usage, makes early diagnosis virtually impossible. We have recently treated two patients with unusual manifestaitons of ergotism, and in neither of these patients was the diagnosis made early in the course of the disease. Our experience with these two patients prompted us to review the history of ergotism as well as the pharmacology and toxicity of the various ergot preparations. This review, together with a description of the clinical course of the two patients, forms the basis of this report.

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Historical Review

The first Western reference to ergotism was in the ninth century A.D. and described an epidemic of gangrenous ergotism wherein "a great plague of swollen blisters consumed the people by a loathsome rot so that their limbs were loosened and fell off before death."[4] Convulsive ergotism was first described in the eleventh century as a "fire which twisted the people."[4] A mixed epidemic with both gangrenous and convulsive manifestations was described later in the eleventh century. Large epidemics of ergotism occurred in Europe, Scandinavia, Bohemia, and Russia from the ninth through the nineteenth century, at which time the frequency declined sharply, although epidemics occurred into this century including a small epidemic in France in 1951.[2,4,23,39,43]

Epidemics of ergotism usually presented purely gangrenous or purely convulsive manifestations, although several mixed epidemics were reported from Russia.[4] A

satisfactory explanation for this repeated observation has never been presented, although hypovitaminosis A has been circumstantially implicated as an etiologic factor in convulsive ergotism.[4,18,50] The latter appears with lower doses of ergot than does the gangrenous form, which may explain death from convulsive ergotism without the appearance of gangrene, but does not explain death from gangrenous ergotism without the appearance of convulsions. Also, inadequately explained is why gangrenous ergotism occurred most frequently in France and only rarely in Germany, where the convulsive form predominated.[4] Possible pharmacologic differences between the ergots of different areas is unproven. A number of factors have been felt to predispose to the development of epidemic ergotism in individual patients, including hypovitaminosis A and C, hepatic disease, malnutrition, reanal disease, sepsis, vascular disease and thyrotoxicosis.[4,8,14,45,50]

In 1676, it was recognized that epidemic ergotism resulted from eating foods, usually breads or cereals, made from rye which was contaminated with the fungus, *Claviceps purpurea*.[4] The sclerotium of this fungus is ergot, and the fungus elaborates the ergot alkaloids as well as several other pharmacologically active compounds, including histamine and tyramine. That ergot epidemics persisted beyond that time appears due in large part to the resistance to change of an uneducated public, and, strikingly, to the defense of ergot by a number of Europe's most learned men.[4]

The earliest Western description of the medicinal use of ergot was in 1582 when it was reported useful as a uterine stimulant.[4] In 1820, ergot was added to the U.S. Pharmacopoeia for obsetetrical use, although the potential toxic effects of the drug were clearly recognized at that time.[4,25,36] The earliest reference to the use of ergot for the treatment of migraine headache was in 1883.[17]

Ergotamine was isolated by Stoll in 1918 and its salt, ergotamine tartrate, proven to be a potent and stable compound which could be chemically assayed.[4,44] Reports of iatrogenic ergotism, almost exclusively attributable to ergotamine, have appeared since that time, including those by Oginz 1930,[41] Gould *et al.* 1936,[26] Yater and Cahill 1936,[50] vonStorch 1938,[45] Thompson *et al.* 1950,[48] Young and Humphries 1961,[51] Hudgson and Hart 1964,[32] and most recently, McLoughlen and Sanders 1972.[38]

Pharmacologic Effects

Naturally occurring ergot contains several pharmacologically active substances other than the ergot alkaloids; however, their role in the production of epidemic ergotism and in the toxicity of whole ergot preparations is unknown. Chemically and pharmacologically the ergot alkaloids are divided into three categories: amino acid alkaloids (ergotamine); dihydrogenated amino acid alkaloids (dihydroergotamine and dihydroergotoxine), and the amine alkaloids (ergonovine).[25,44]

The major pharmacologic effects of the ergot alkaloids include smooth muscle stimulation, central sympatholytic activity, and peripheral alpha adrenergic blockade. Smooth muscle stimulation is most evident as vasoconstriction and as uterine contraction. Vasoconstriction appears to result from stimulation of the alpha receptors to which the drug is tightly bound, while uterine contraction results from direct smooth muscle stimulation exclusive of the alpha receptors.[33] While all of the ergot preparations, except the amine alkaloids, are bound to the alpha receptors, the ability of the various preparations to produce alpha receptor stimulation varies widely.

The central sympatholytic property results from drug action directly on the medullary vasomotor centers and occurs with lower drug dosages than are required for peripheral alpha receptor blockade.[20,21] Other effects upon the central nervous system include the stimulation of emesis and the inhibition of prolactin secretion.[6,19,22,25]

The amino acid alkaloids (e.g., ergotamine) are the most potent vasoconstrictors, displaying no oxytocic effects when given orally. This class of drugs has been most widely used in the treatment of migraine headache. The amine alkaloids (e.g., ergonovine and methylergonovine) are potent oxytocics with relatively weak vasoconstricting actions and no sympatholytic or alpha blocking properties.[25] A summary of the pharmacologic actions of the various ergot preparations is presented in Table 1.

TABLE 1. *Pharmacologic Properties of Ergot Derivatives*

Class	Action			
	Vasconstriction	Oxytocic	α-Blocker	Sympatholytic
Amino Acid Alkaloids (Ergotamine Tartrate)	Most Active	Highly Active but of Delayed Onset, Not Active Orally	Active	Active
Dihydrogenated Amino Acid Alkaloids (Dihydroergotamine)	Active but less than Above	Active on Pregnant Human Uterus	Most Active	Most Active
(Dihydroergotoxine)	None			
Amine Alkaloids (Ergonovine and Methylergonovine)	Slight	Most Active	None	?

Toxicity

The most important toxic effect of the ergot alkaloids is vasospasm which can effect virtually any vessel, including the coronary arteries and the splanchnic circulation.[3,5,16,24,33,35,45] Prolonged vasospasm is expressed clinically as ergotism of either the gangrenous or convulsive types, or rarely as both. Symptoms common to both forms of ergotism include lassitude, emesis, lumbar muscle pain, ischemic cutaneous vesicles on the hands or feet, diarrhea, and impaired mental function.[4] The following descriptions of the two forms of ergotism are derived from observations made during the great epidemics when the victims had ingested a mixture of ergots plus other substances of unknown significance. There have been far fewer observations of patients with ergotism resulting from the ingestion of a pharmacologically pure substance, but these observations would generally agree with the classic descriptions. The notable exception is that convulsive ergotism has not been reported following the use of pure ergot compounds, although Oginz noted a report in the German literature of a patient who developed acute pseudotabes dorsalis while receiving fluid extract of ergot containing ergotamine tartrate and unknown other substances.[40,41] This resolved when the ergot was withdrawn.

Gangrenous ergotism is characterized by pulseless ischemic limbs which may be covered with blisters. If ergot ingestion continues, the patient develops dry gangrene which may lead to autoamputation or, less commonly, suppurative gangrene and sepsis. This is frequently preceded by weeks of intense burning pain known as St. Anthony's fire, although in cases of massive intoxication as little as 24 hours may elapse between ergot ingestion and the onset of gangrene. Although the lower extremities are most often affected, the upper extremities may be involved as well, and occasionally may be the only extremities affected.[7,10,12,17,32] The ischemic process is usually symmetric, although unilateral limb involvement has been reported.

Symptomatic vasospasm, although most common in the extremities, may affect any organ system. Severe splanchnic vasospasm may occur, occasionally with the production of intestinal infarction.[4,5] Renal artery vasoconstriction may be sufficiently severe to present as acute renal failure.[16] Coronary artery vasoconstriction may become manifest as angina pectoris, or, rarely, as acute myocardial infarction.[24,42,45] Ophthalmic artery vasospasm has been described occasionally with the clinical symptoms of transient or permanent blindness.[4,36]

Convulsive ergotism in its most severe form is characterized by repeated grand mal seizures leading to death. Milder forms are characterized by formication, an apparently invariable symptom in this condition. Increasing intoxication leads to clonic contractions of digits, or entire extremities, accompanied by severe pain. Chronic weakness, contractures, pain, hemiparesis, paraplegia, pseudotabes dorsalis and sensory disturbances including anesthesia of the extremities may occur and are frequently permanent. Mental disturbances ranging from transient disorientation to permanent dementia have been described. A number of ophthalmic complications have been reported following convulsive ergotism, including mydriasis, amblyopia, cataracts, retinal damage, optic nerve damage and glaucoma.[13,15,36]

Although gangrenous and convulsive ergotism share certain symptoms, the two are usually clinically distinct. Gangrenous erogtism is rarely accompanied by convulsions and convulsive ergotism is rarely accompanied by gangrene, although in both types, a common pathologic abnormality is severe vasospasm. If this persists, proliferation of the endothelium and thrombosis may occur. This may be accompanied by hyaline degeneration and fibrosis of the vascular wall, apparently resulting from loss of vascular wall nutrition from luminal blood flow as well as from spasm of the vasa vasora.[26,35,48,50] Direct neurotoxicity has not been described and the neurologic manifestations are thought to be secondary to ischemia.[3,4,30,35,45,50] Hemorrhagic infarction of the brain and degeneration of the posterior and lateral columns of the spinal cord have occurred rarely.[50]

Case Reports

Case I. A 61-year old Caucasian female presented to our emergency room with a three-week history of severe pain in both lower extremities. The patient was a known alcoholic with documented mild chronic liver disease. Her legs were noted to be cool and moderately cyanotic with delayed capillary filling and diminished sensation of both feet. No pulses could be palpated in either lower extremity below the femoral artery. The patient's hands were cool and moderately cyanotic and no pulses could be palpated distal to the brachial artery in either arm. The patient had been examined six weeks earlier in the Outpatient Clinic at which time she was noted to have normal pulses to palpation in all extremities and a normal neurologic examination. The patient denied the use of drugs. She was admitted to the hospital with a diagnosis of possible vasculitis. Twenty-four hours later angiography was performed revealing diffuse, severe vascular spasm (Fig. 1A). Upon repeat specific questioning, the patient reluctantly admitted using two Cafergot[R]* suppositories daily for the preceding three weeks for headache.

Two days following admission her peripheral pulses were all normal to palpation; however, at this time she manifested bilateral foot drop as well as diminished pain, temperature, vibration, and position sensation in both legs. A bone marrow examination revealed no megaloblastic changes. Lower extremity nerve conduction and electromyographic determinations were performed and showed no conduction in the deep peroneal nerves and fibrillation potentials in the extensor brevis muscles bilaterally. The patient was maintained on bed rest and within two weeks had totally

* Cafergot[R] (Sandoz). Each suppository contains ergotamine tartrate 2.0 mg and caffeine 100 mg.

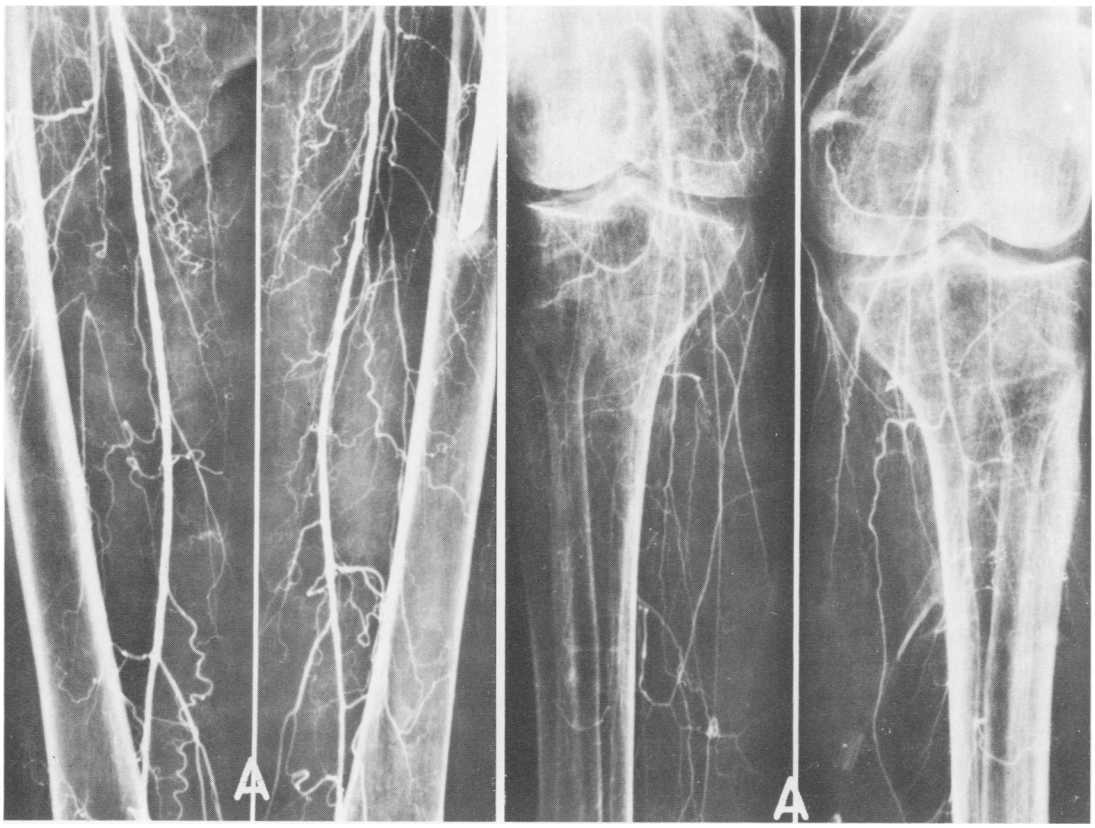

FIG. 1A. Arteriogram of first patient 24 hours after hospital admission. Moderate narrowing of the superficial femoral artery is present, with marked spasm of the popliteal artery and almost total obliteration of the branches of the popliteal trifurcation.

healed the superficial foot ulcers and showed some improvement in the bilateral foot drop. A repeat arteriogram was normal (Fig. 1B). Repeat nerve conduction determinations and electromyography at monthly intervals demonstrated progressive reinervation. At three months, the foot drop had totally resolved and the patient had normal sensation over the feet, although she complained of severe dysesthesias in both lower extremities.

Case II. A 34-year-old Caucasian male was referred to our institution for evaluation of suspected peripheral vascular disease. The patient had a five-year history of temporal headaches, thought to be histamine cephalgia, for which he had been taking two or three Cafergot[R] suppositories daily for several months. Prior to this he had taken 8–10 suppositories weekly for two years. He presented to his local physician with a three-week history of left leg pain which had progressed to severe claudication on minimal exertion. Physical examination revealed no pulses palpable distal to the left femoral artery. Femoral arteriography was performed and showed severe vasospasm of the left femoral artery with no evidence of atherosclerotic obstruction. Ergotism was not suspected, and the patient continued to take the ergot suppositories. Despite continued use of ergot, the left leg improved partially; however, one day prior to admission to our institution, he noted the sudden onset of blurred vision in his left eye, followed by a total loss of vision in the eye. He underwent a complete ophthalmologic examination on the same day and was noted to have severe retinal vasospasm and retinal pallor. A central scotoma was documented and the visual acuity was found to vary between 20/200 and 20/400. When the patient arrived at our hospital the next day, he was still complaining of left leg pain as well as blurred vision in his left eye, although he felt both were improving slightly.

On examination all pulses were palpable although quite weak in both arms and in the right leg. Only a weak femoral artery pulse could be palpated in the left leg with no pulses palpable distally. The use of the Cafergot[R] suppositories was discontinued, and 24 hours later a repeat complete ophthalmologic examination was normal. Within 48 hours all pulses were normal to palpation, including the previously absent left popliteal, posterior tibial, and dorsalis pedis pulses. The patient's severe headaches continued daily requiring narcotics for relief. Over the next several weeks, the headaches decreased dramatically in severity, requiring only occasional codeine tablets. His left leg symptoms resolved completely. On his most recent examination, six months following discharge, he was totally asymptomatic except for mild occasional headaches requiring the use of one to three codeine tablets per week.

Discussion

Both patients were taking massive overdoses of ergotamine tartrate, as can be seen from Table 2 which lists the manufacturer's maximal recommended dosage for the various routes of administration. The first patient had used 28 mgm of ergotamine tartrate by rectum weekly for three weeks without having previously used the drug. She developed acute toxicity after three weeks of usage, although this was not initially appreciated because of her denial of drug usage. The second patient had used 28–42 mgm of ergotamine tartrate by rectum weekly for several months, and prior to that time, he had used 20 mgm or more per week for several years. He had never developed any toxic symptoms until about three weeks before admission to our hospital. These examples

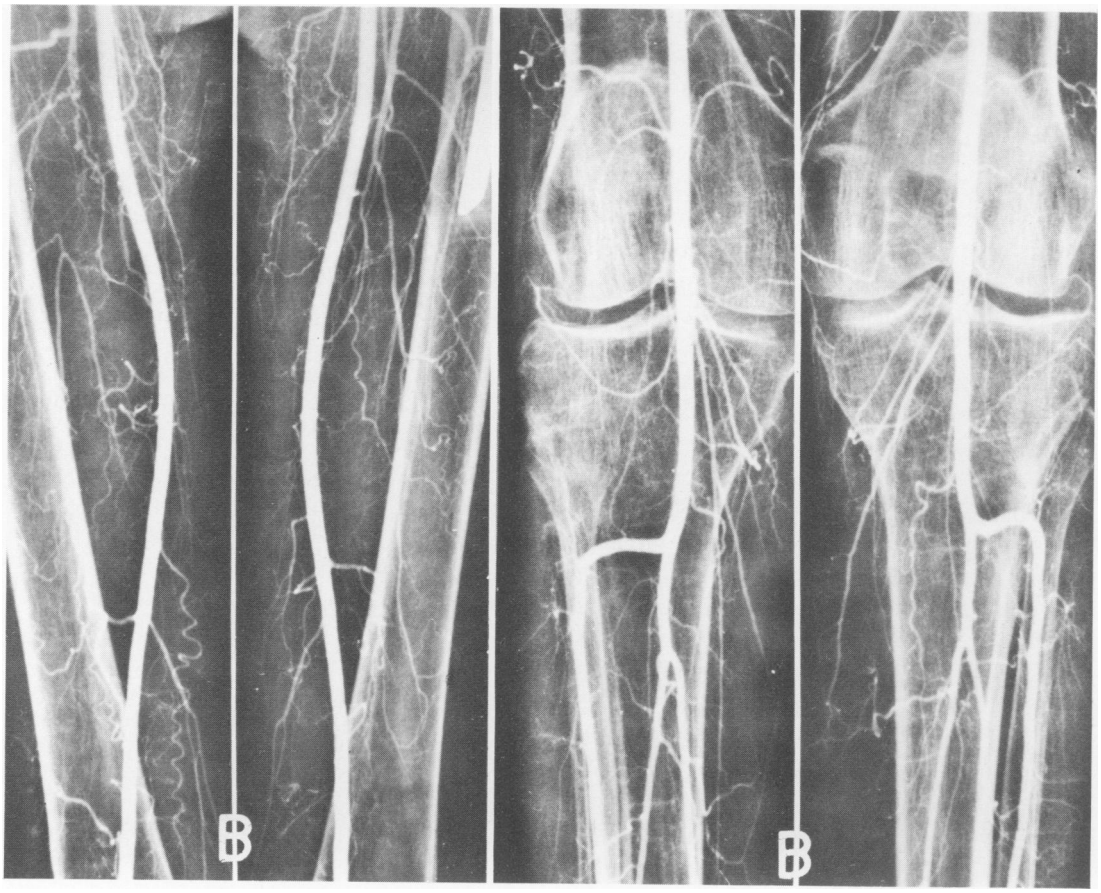

FIG. 1B. Normal arteriogram two weeks later on same patient as in Fig. 1A.

clearly illustrate the tremendous variability in ergot tolerance among patients. It has long been recognized that some patients are quite sensitive to ergots, while others tolerate doses considered to be in the toxic range for years without developing symptoms. An unresolved question is why a patient who has tolerated large doses of ergot for a prolonged period of time should suddenly develop symptoms of intoxication. The actual incidence of ergot intoxication has been estimated at less than 0.01% of patients taking ergot preparations, although side effects such as nausea, vomiting, abdominal and leg pain occur in about 10% of patients taking ergots orally or rectally.

The initial presentation of the first patient with symmetric ischemia worse in the lower extremities is typical of gangrenous ergotism, although she rapidly developed peripheral neurological symptoms. The development of bilateral foot drop with no evidence of nerve conduction followed by return to normal in three months is strong evidence of peripheral ischemic neuropathy. Although peripheral nerve damage has been described in epidemic ergotism, there has been no previous report of reversible foot drop following natural or iatrogenic ergotism.

The second patient's presentation with unilateral lower extremity ischemia is unusual, but has been previously reported, as has the spontaneous improvement of limb ischemia despite the continued use of ergots.[17,42] The visual symptoms and findings are rarely seen, but appear similar to those described by Kravitz in 1935 and by Gupta more recently.[27,36] However, the lesion spared the optic nerve in our patient and involved the nerve in the two previous reports. This patient also demonstrated the phenomenon of rebound headache which has been frequently described following the withdrawal of ergots. Most patients treat this rebound headache with additional ergot, to which they usually respond, and in so doing perpetuate an unrelenting cycle which may end in ergotism. Complete ergot withdrawal usually produces severe headaches for about five days at which point they usually subside.[19,42]

Both patients were diagnosed following angiography, a situaiton which has been reported by others.[16,30,34,38,45,47] The angiographic findings of ergotism as first de-

TABLE 2. *Dosage for Ergotamine Tartrate**

Route	Single Dose	Maximum Per Attack	Maximum Per Week
Oral	1 mg	6 mg	11 mg
Rectal	2 mg	4 mg	8 mg
Parenteral	0.25–0.5 mg		1.0 mg

* Sandoz.

scribed by Yater and Cahill in 1936 when they reported "the main arteries of the leg to be smooth in outline and apparently normal down to the lower third of the leg when they faded out into a point" were present in both patients.[50] These authors also noted collaterals around the vasospastic segment. These collateral vessels have been observed by others and have been noted to disappear following dilatation of the major vessel upon withdrawal of ergots.[12,13,28,34] Recent reports of the angiographic findings of ergotism have confirmed the original description.[1,13,16,24,28,37,47,49,51]

The treatment of both these patients was entirely expectant, and they both improved within a few days as the drug was metabolized. Others have reported similar results.[13,14,25,26,31,43,47] Numerous pharmacologic agents have been used in an effort to achieve vasodilatation. These include ethyl alcohol, amyl nitrite, scopolamine, theophyllin, tolazoline, hydergine, phentolamine, sodium nicotinate, papaverine, procaine, and lidocaine.[1,7–12,16,26,29,30,32,38,48] None of these has been of any immediate clinical benefit except for sodium nicotinate and tolazoline, and the benefits from these drugs have been confined to single case reports.[46,48,51] Direct sympathetic blockade using conduction anesthetic techniques has occasionally appeared to be of some benefit, as has the performance of regional sympathectomy.[32,37,38]

It is difficult to understand how vasodilatation could result from the use of vasodilating drugs or sympathectomy since ergotamine is tightly bound to the alpha receptors. Attempts to experimentally displace ergotamine from the alpha receptors with phenoxybenzamine have been unsuccessful.[33] In addition, it has long been recognized that ergotamine is a pure vasoconstrictor in the sympathectomized limb.[6] Anticoagulation with heparin or the use of dextran may be of benefit, since thrombosis may occur in the spastic vascular segments.

We feel that the initial treatment of ergot intoxication should be the simple discontinuation of the ergot preparation. If there appears to be impending tissue loss, it would appear reasonable to use heparinization and/or dextran and intra-arterial tolazoline or intravenous sodium nicotinate. If there is no response to these measures, regional sympathetic blockade may be attempted, although as noted, there is no firm evidence that this is beneficial.

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